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An evidence-based approach to managing seizures associated with fever in children

A previously healthy 19-month-old boy is rushed to the emergency department (ED) after he was found unconscious at home by his mother. As she went to wake him from his afternoon nap, she heard a short cry. She found him lying on his back, rigid and unresponsive, apparently not breathing, and with blue lips. On arrival in the ED, his breathing and circulation were adequate. His pulse rate was 110

beats per minute, his blood pressure was 100/60 mm Hg, and his temperature was 39.9 °C (103.8 °F). On examination, the boy is lethargic and confused but seems to recognize his mother. Apart from slight redness of the pharynx, there is no obvious focus of infection and no rash. Neck rigidity is difficult to evaluate because he actively resists examination and refuses to sit.

BACKGROUND

A febrile seizure is defined as a seizure occurring in a neurologically healthy child between 6 months and 5 years of age. Simple febrile seizures are brief (<15 minutes), generalized, and occur in association with fever and only once during a 24-hour period.¹ Seizures occurring in association with fever are the most common neurologic disorder in pediatrics and affect 2% to 4% of all children in Great Britain and the United States.² Children whose seizures are attributable to a central nervous system infection and those who have had a previous afebrile seizure or central nervous system abnormality are not considered to have simple febrile seizures.

A number of questions arise from the scenario (see box). You wish to use an evidence-based approach, so you frame your questions to maximize the yield of a literature search and look first for high-quality systematic reviews and evidence-based practice guidelines to answer these questions.

Using the subject heading “febrile seizures” in The Cochrane Library, you find the abstracts of 2 systematic reviews in the *Database of Abstracts of Reviews of Effectiveness* (DARE) and 18 articles in the *Central Cochrane Controlled Trials Register* (CENTRAL/CCTR). You also search MEDLINE using the Clinical Queries feature.

WHAT IS THE LIKELIHOOD THAT THE CHILD HAS MENINGITIS?

You look for cross-sectional or follow-up studies of children with seizures and fever that identify children who developed meningitis. Your Clinical Queries search nets 22 articles, most of which are informal reviews and letters. One article, a decision analysis, appears relevant.³ Then, clicking on the “Related Articles” hyperlink next to this reference elicits 2 more articles that appear to be relevant surveys.^{4,5}

Wears et al reviewed 7 studies performed in urban hospital EDs in the United States.⁴ All studies were retrospective surveys of medical records that documented the disease outcome after a seizure with fever. Among 2,100 cases of seizures associated with fever, an overall meningitis prevalence of 1.2% was found, ranging from 0% to 4% within the 7 studies. However, we do not know whether all children underwent lumbar puncture in these EDs or whether meningitis was excluded on clinical grounds at follow-up.

In the second study, 7% of the children who visited the ED of 2 Dutch hospitals and who had a first seizure associated with fever had either bacterial or viral meningitis.⁵ Because this study was done in a hospital setting in a country where general practitioners manage as much as 50% of all cases of seizure with fever,^{6,7} its results may not be applicable to the situation in which there is no family

Summary points

- Seizures occurring in association with fever affect about 4% of all children
- In children with a seizure associated with fever, the probability of bacterial meningitis is low but not zero (between 0% and 4%); unremarkable findings on physical examination and history make bacterial meningitis highly improbable
- After a first febrile seizure, the probability of seizure recurrence in subsequent fever episodes is related to the child's age—being highest for children aged between 1 and 3 years
- After a first febrile seizure, prophylactic treatment with antiepileptic drugs does not decrease the likelihood of future febrile seizures; the likelihood of future afebrile seizures is low and is determined by the presence or absence of risk factors

physician or general practitioner to evaluate a child before referral to a hospital.

From these 2 studies, it can be concluded that the prevalence of meningitis among children with seizures and fever in North American pediatric EDs is between 1% and 2% and, through selective referral, may be as high as 7% in a European country. These figures indicate that a large number of “unnecessary” lumbar punctures would be done if a lumbar puncture was performed in all children with a seizure associated with fever.

Questions for focusing a literature search

- **Baseline risk** In young children with a seizure associated with fever (patient or population, event), what is the probability of bacterial meningitis (outcome)?
Database: MEDLINE (PubMed); terms: *fever seizures meningitis, etiology, sensitivity*
- **Diagnosis** In young children with a seizure associated with fever (patient or population, event), can unremarkable results of a physical examination and history (intervention or test) reliably exclude bacterial meningitis (outcome)?
Database: MEDLINE (PubMed); terms: *fever AND seizures AND meningitis AND (clinical signs OR diagnosis)*
- **Therapy** In children with a first febrile seizure (patient or population, event), can prophylactic treatment with antiepileptic drugs (intervention) compared with no therapy (comparison) decrease the likelihood of future febrile seizures (outcome)?
Database: PubMed; terms: *seizures AND fever AND recurrence (therapy)*
- **Prognosis** In children with a first febrile seizure (patient or population, event), what is the likelihood of future febrile or afebrile seizures (outcome)?
Database: PubMed; terms: *seizures AND fever AND epilepsy (prognosis)*

CAN A SEIZURE BE THE SOLE MANIFESTATION OF MENINGITIS IN AN APPARENTLY WELL CHILD?

You look for studies that investigate the relationship of various signs and symptoms with meningitis in children with seizures and fever, preferably in the form of likelihood ratios (LRs). Only 1 study is found that actually provides sensitivity, specificity, and LRs for the various clinical indicators of meningitis.⁵ This study tried to identify criteria, based on age, specific clinical indicators, or the results of initial blood tests, that could serve as indications for performing lumbar puncture. Among 309 children aged 3 months to 6 years consecutively seen with a first seizure associated with fever in the ED of 2 major children's hospitals in the western part of the Netherlands, 23 cases of meningitis (7%) were diagnosed. These 23 cases were then compared with a reference group of 69 children with seizures associated with fever, but without meningitis, selected at random from the remaining 286 children.

Several clinical signs and symptoms were examined for their ability to differentiate children with from those without meningitis. The clinical "risk factors" shown in table 1 were evaluated. The presence of petechiae, nuchal rigidity, and/or coma identified 16 (70%) of the 23 children with meningitis. In children who did not have meningitis, these "major" signs of the disease were not found; the LR when any of these signs is present (LR+) is, therefore, infinite (95% confidence interval [CI], 6.0 to infinity), and the meningitis probability approaches 100% (95% CI, 31%-100%). In the absence of meningeal irritation, petechiae, or complex features of the seizure, there were no meningitis cases in the study. The child's age, sex, degree of fever, and results of routinely performed blood tests did not have any diagnostic value. The likelihood ratios of the negative and positive test can separate children into 2 groups: 1 group in whom the risk of meningitis is high and who should have a lumbar puncture regardless of other history or physical findings, and 1 group in whom the risk of

meningitis is low and for whom other clinical findings should be used in the decision to tap.

This was a retrospective review of the medical records of children presenting with a first episode of seizure and fever. The study group was limited to children aged 3 months to 6 years with first-time seizure and fever. The pretest probability of meningitis is likely to be different in another group of children. In addition, nuchal rigidity may not be as strong a predictor in young children; in this patient group, the mean age was 18 months. However, these results indicate that it is indeed unusual for a child with meningitis to present only with a seizure. Also, a fair number of children without meningitis will present with the risk factors mentioned above—that is, the specificity of these "clinical tests" is far from 100%.

WILL PROPHYLACTIC TREATMENT WITH ANTIEPILEPTIC DRUGS DECREASE THE LIKELIHOOD OF FUTURE FEBRILE SEIZURES?

You look for studies in which patients with febrile seizures were randomly allocated to different treatment regimens and observed over time to see how many had subsequent febrile seizures. Of the more than 200 articles uncovered from your search, 5 specifically address your question and are either meta-analyses of randomized controlled trials (RCTs) or are RCTs.⁸⁻¹²

Newton assessed the efficacy of phenobarbital and valproate sodium for the prophylactic treatment of febrile convulsions by summarizing the results from all 8 British clinical trials that were done before 1988.⁸ Data were pooled and analyzed on an intention-to-treat basis. The overall odds ratio (OR) of recurrent febrile seizures for phenobarbital was 0.8 and for valproate, 1.42. Neither result was statistically significant. The author, therefore, concluded that neither treatment is to be recommended.

A second meta-analysis summarized 4 published non-British RCTs that had been done up to 1996 in which

Table 1 Discriminating ability of combinations of clinical indicators of meningitis among children with a seizure associated with fever. Likelihood ratios (LRs) with 95% confidence interval (95% CI) for the presence (LR+) and absence (LR-) of combinations*

Combination of indicators	Cases (n = 23), no. (%)	Referents (n = 69), no. (%)	LR – (95% CI)	LR+ (95% CI)
At least 1 complex feature†	17 (74)	26 (38)	0.4 (0.2–0.8)	1.9 (1.3–2.9)
At least 1 history feature‡	18 (78)	32 (46)	0.4 (0.2–0.9)	1.7 (1.2–2.4)
Either a complex or a history feature	23 (100)	45 (65)	0 (0–1.0)	1.5 (1.3–1.8)
At least 1 "major" sign§	16 (70)	0 (0)	0.3 (0.2–0.6)	∞ (6.0–∞)
At least 1 "minor" sign	5/7 (71)	24 (35)	0.4 (0.1–1.4)	2.1 (1.2–3.6)

*From Offringa et al.⁵

†Complex seizure features: partial, multiple, or prolonged seizure (ie, >15 minutes).

‡History features: febrile illness for at least 3 days, vomiting or drowsiness at home, and a physician's visit in the previous 48 hours.

§"Major": petechiae, definite nuchal rigidity, and coma.

||"Minor" signs of meningitis, after exclusion of children with any "major" signs: dubious nuchal rigidity, persisting drowsiness, convulsions, or paresis or paralysis on examination in the emergency department.

phenobarbital was used as a preventive treatment of febrile seizures.⁹ The risk of recurrences was lower in children receiving continuous phenobarbital therapy than in those receiving placebo (OR, 0.54; 95% CI, 0.33-0.90). On average, 8 children would have to be treated continuously with phenobarbital for 2 years to prevent 1 febrile seizure (number needed to treat=8; 95% CI, 5-27).¹³ However, because of the adverse effects of phenobarbital use, such as irritability, hyperactivity, and somnolence, and possible diminished cognitive development,¹⁰ Farwell et al also concluded that phenobarbital prophylaxis of febrile seizures cannot be recommended.

To avoid the side effects of continuous antiepileptic drug therapy, rapid-acting anticonvulsant agents given only during fever periods have been used in an attempt to reduce the risk of recurrent febrile seizures. Phenobarbital given during fever has been ineffective, probably because of the delay in achieving appropriate serum and tissue levels. Thus far, only prophylactic diazepam, given orally or rectally, has been studied in placebo-controlled trials.

Rosman et al conducted a double-blind RCT among 406 children with a mean age of 24 months who had at least 1 febrile seizure, and they compared the use of diazepam (0.33 mg/kg of body weight), administered orally every 8 hours during febrile illnesses, with that of placebo.¹¹ During a mean follow-up of 2 years, the relative risk of subsequent febrile seizures per person-year was 0.56

(95% CI, 0.38-0.81). Many parents did not give the study medication as directed; an analysis restricted to children who had seizures while actually receiving the study medication showed an 82% reduction in the risk of febrile seizures with the use of diazepam. Between 25% and 30% of the children in the study by Rosman et al were irritable, lethargic, or had ataxia after taking diazepam, which may interfere with the ability of parents and clinicians to distinguish benign childhood febrile illness from more serious disease. For every 3.5 to 4 children who were given diazepam, 1 developed these symptoms (number needed to harm=3.4-4.0). The decision to recommend this treatment will depend on balancing these possible harms against the possible benefits to each specific child and the values of the child's family.

IS INTERMITTENT ANTIPYRETIC TREATMENT EFFECTIVE IN PREVENTING SEIZURE RECURRENCE?

In an RCT conducted in the Netherlands,¹² children aged 1 to 4 years who had at least 1 risk factor for febrile seizure recurrence (table 2) were randomly assigned to either ibuprofen syrup, 5 mg/kg of body weight per dose, or placebo, to be administered every 6 hours during fever (defined as a temperature higher than 38.4 °C [101.1 °F]). Median follow-up time was 12 months. The relative risk of recurrence in the group receiving ibuprofen was not significantly different from that in the placebo group.

Table 2 Summary of the evidence

Question	Type of evidence	Result	Comment
What is the probability of bacterial meningitis after a seizure associated with fever?	Summary of surveys of children seen in EDs	0.2%-7%, depending on health care system and setting	English and Dutch general practitioner referral system will select children with a higher risk to present to an ED
Can unremarkable findings of a physical examination and history reliably exclude bacterial meningitis?	Case-referent study evaluating risk factors	In the absence of focal, prolonged, or multiple seizures; suspicious findings on physical examination (petechiae and signs of circulatory failure); and abnormal neurologic findings (signs of meningeal irritation and various degrees of coma), meningitis could be ruled out	Unusual for a child with meningitis to have only a seizure
Can prophylactic treatment with continuous antiepileptic drugs, intermittent oral diazepam, or an antipyretic drug decrease the likelihood of future febrile seizures?	2 systematic reviews of RCTs, 2 RCTs	Continuous antiepileptic drugs, intermittent diazepam, or antipyretics did not reduce the recurrence rate	2 meta-analyses had same results; lack of effectiveness and side effects limit the use of intermittent oral or rectal diazepam
What is the likelihood of future febrile or afebrile seizures?	Synthesis of 5 cohort studies with risk factor analyses and 1 cohort study	Most important factor is child's age, the presence of a first-degree relative with febrile or unprovoked seizures increases recurrence risk	Variation in recurrence risk is related to the presence of risk factors; complex features to the seizure do not predict recurrence of febrile seizures but are associated with an increased risk of epilepsy

EDs = emergency departments; RCTs = randomized controlled trials.

WHAT IS THE RISK OF RECURRENT FEBRILE AND UNPROVOKED SEIZURES?

To address the parents' concerns about the prognosis, you look for a large cohort of patients with a new onset of simple febrile seizures who have been observed over time to see how many develop recurrent febrile and nonfebrile seizures. Your search strategy yields 26 articles, 2 of which meet your study design criteria.^{14,15}

In a collaborative study, the individual data from 5 follow-up studies that used similar definitions of febrile seizures and risk factors were pooled and reanalyzed¹⁴ to estimate the risk of frequent recurrent seizures and the occurrence of complex seizures in previously healthy, untreated children. Of 2,496 children with 1,410 episodes of recurrent seizures, 32% had 1, 15% had 2, and 7% had 3 or more recurrent seizures after a first febrile seizure; 7% had a complex recurrence. The hazard of recurrent seizures was highest for children between the ages of 12 and 24 months. A history of febrile or unprovoked seizures in a first-degree family member, a relatively low temperature at the first seizure, young age at onset (<12 months), a family history of unprovoked seizures, and a partial initial febrile seizure were all associated with an increased risk of subsequent complex seizures. Although complex features of the first seizure—that is, partial, multiple, or seizure longer than 15 minutes—have long been thought to predict recurrence, the follow-up studies included in this review showed that only multiple initial seizures are associated with a 1.6-fold increase in risk for a first recurrence.¹⁴ Prolonged or focal initial seizures were not associated with this increased risk, as long as they had not led to permanent neurologic abnormalities.

In a cohort of 428 children observed prospectively for at least 2 years from their first febrile seizure, risk factors for the occurrence of unprovoked seizures were assessed.¹⁵ Unprovoked seizures occurred in 26 children (6%). Neurodevelopmental abnormalities, complex febrile seizures, and a family history of epilepsy were associated with an increased risk of unprovoked seizures. Recurrent febrile seizures and a brief duration of fever before the initial febrile seizure were also risk factors. A family history of febrile seizures, temperature and age at the initial febrile seizure, sex, and race were not associated with unprovoked seizures. This high-quality evaluation of predictors gives insight into the risk of epilepsy and may be used to counsel patients. However, no studies have examined the possibility of preventing epilepsy with pharmacologic interventions after a first or a second febrile seizure.¹⁵⁻¹⁷

Application of the evidence to the scenario
Given the history and the physical examination, this child can be considered at a low risk of meningitis, and you decide to observe him

without doing a lumbar puncture. After the acute episode resolves, you reassure the parents and counsel them regarding the risk of future seizures. For this child, the probability of frequent or possibly threatening recurrences is low. The evidence does not support using a daily anticonvulsant drug like phenobarbital or valproate, and the intermittent use of diazepam or an antipyretic agent during fever is not effective in preventing seizure recurrence. You will need to spend time with the parents to help them overcome the fears and anxiety that seizures provoke and educate them about the natural history of febrile seizures and their consequences. They may still request treatment with anticonvulsant agents. This will depend on the values that they place on different outcomes such as subsequent seizure and the adverse effects of anticonvulsant use. You counsel the parents that the risk of recurrence declines rapidly after 6 months from the previous seizure and instruct them to position the child for optimal airway patency in case of a new seizure, which is especially important if the child vomits. A prescription for rectal diazepam should also be given and the parents instructed in how to administer it in the rare case of a lengthy recurrence—that is, a seizure that goes on for more than 15 minutes.^{18,19} This approach has been suggested to also reduce parental fear.²⁰

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Sponsorship, authorship, and accountability

The editors of *wjm* along with editors of other general medical journals recognize that the publication of clinical findings in respected peer-reviewed journals is the ultimate basis for most treatment decisions. Public discussion about this published evidence of efficacy and safety rests on the assumption that clinical data have been gathered and are presented in an objective and dispassionate manner. This discussion is vital to the practice of medicine because it shapes treatment decisions made by physicians and drives public and private health care policy. We are concerned that the current intellectual environment in which clinical research is conceived, study subjects are recruited, and the data analyzed and reported (or not reported) may threaten this precious objectivity.

Until recently, academic, independent clinical investigators were the key players in design, patient recruitment, and data interpretation in clinical trials. The intellectual and working home of these investigators, the academic medical center, has been at the hub of this enterprise, and many institutions have developed complex infrastructures devoted to the design and conduct of clinical trials.^{1,2} But as economic pressures mount, this may be a thing of the past.

As trials have become more sophisticated and the margin of untreated disease harder to reach, the size of the trials and, consequently, the costs of developing new drugs have greatly increased. It is estimated that the average cost of bringing a new drug to market in the United States is about \$500 million.³ The pharmaceutical industry has recognized the need to control costs and has discovered that private non-academic research groups—ie, contract research organizations (CROs)—can do the job for less money and with fewer hassles than academic investigators. Over the past few years, CROs have received the lion's share of clinical-trial revenues. For example, in 2000 in the United States, CROs received 60% of the research grants from pharmaceutical companies, compared with only 40% for academic trialists.¹

As CROs and academic medical centers compete head to head for the opportunity to enroll patients in clinical trials, corporate sponsors have been able to dictate the terms of participation in the trial, terms that are not always in the best interests of academic investigators, the study participants, or the advancement of science generally.⁴ Investigators may have little or no input into trial design, no access to the raw

data, and limited participation in data interpretation. These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they do not, the sponsor will find someone else who will. And, unfortunately, even when an investigator has had substantial input into trial design and data interpretation, the results of the finished trial may be buried rather than published if they are unfavorable to the sponsor's product. Such issues are not theoretical. A number of recent examples of such problems have been made public, and we suspect that many more go unreported.^{5,6}

We strongly oppose contractual agreements that deny investigators the right to examine the data independently or to submit a manuscript for publication without first obtaining the consent of the sponsor. Such arrangements not only erode the fabric of intellectual inquiry that has fostered so much high-quality clinical research, but also make medical journals party to potential misrepresentation because the published article may not reveal the extent to which the authors were powerless to control the conduct of a study that bears their names.

The section on publication ethics in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*, a document developed by the International Committee of Medical Journal Editors (ICMJE) and widely used by individual journals as the basis for editorial policy, has been fully revised. The revised section may be found linked to this article on our web site (www.ewjm.com).

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